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Research paper

Disrupted orbitomedial prefrontal limbic network in individuals with later-life depression ☆

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ABSTRACT

Background: Depression in old age is an increasing contributor to poor health and accompanying health care costs. Although there is an abundance of literature on later-life depression (LLD), the neural correlates have not been clarified. The aim of this study was to determine whether patients with LLD show abnormal gray matter volume (GMV) and white matter integrity by using multiple image analysis methods.

Methods: The study included 45 patients with LLD and 61 healthy participants who were matched for age, sex, years of education, and vascular risk factors. GMV was examined using voxel-based morphometry, while the white matter integrity was determined by tract-based spatial statistics and tract-specific analysis, which were obtained from high-resolution magnetic resonance images.

Results: Patients with LLD showed significantly less GMV in the orbitofrontal cortex, anterior cingulate, insula, amygdala, and temporal regions, as well as higher fractional anisotropy in the uncinate fasciculus, compared with healthy participants. Patients with LLD who had reduced orbitofrontal and insular GMV had more severe clinical variables. The reduced orbitofrontal GMV was associated with higher fractional anisotropy in the uncinate fasciculus.

Limitation: The effects of medication should also be considered when interpreting the results of this study.

Conclusion: Our results suggest that regional GMV is linked to white matter integrity of the uncinate fasciculus in the orbitomedial prefrontal limbic network, and the disruption of this network may be involved in the pathophysiology of LLD.

1. Introduction

The World Health Organization suggests that the prevalence of depression in older adults is estimated to be 7% (http://www.who.int/mediacentre/factsheets/fs381/en/#) and warned that people with LLD are often overlooked and tend to go untreated because the symptoms coincide with those of other problems of aging. The clinical features associated with LLD, including low response to therapy, high burden on caretakers and high suicide rate (Alexopoulos, 2005), occur because LLD is intricately intertwined with the psychosocial and biological factors of aging (Vu and Aizenstein, 2013). Depression in old age contributes to poor health and increased health care costs. Although there is an abundance of

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Table 1
Demographic and clinical characteristics of the participants.

	Patients with LLD (N=45)			Healthy participants (N=61)			Statistics
	Mean	SD	Range	Mean	SD	Range	*p*
Age (years)	60.2	8.2	50–80	62.9	7.6	50–83	0.078
Sex (M/F)[a]	19/26			17/44			0.123
Years of education (years)	13.3	2.3	9–17	13.6	2.3	9–20	0.488
SIGH-D	17.3	9.7	0–34	0.8	1.1	0–5	< 0.001
Beck depression inventory	24.8	13.5	1–56	7.2	4.72	0–25	< 0.001
GAF	62	16.3	33–100	92.9	4.7	80–100	< 0.001
Vascular risk factors	1.4	0.5	1–3	1.3	0.5	1–3	0.529
MMSE	28	2.2	25–30	28.8	1.7	24–30	0.11
Age of onset illness (years)	49.6	12.9	20–73				
Length of illness (years)	10.6	11	0–45				
Number of episodes	2.5	2.2	1–10				
Imipramine equivalent (mg)	161.2	129.7	0–650.0				

LLD, Late-life depression; SD, Standard deviation; M, Male; F, Female; SIGH-D, Structured Interview Guide for the Hamilton Depression Rating Scale; GAF, Global Assessment of Function; MMSE, Mini Mental State Examination.

[a] *p* Value was analyzed by the chi-squared test. All other analyses utilized Student's *t*-test.

literature on later-life depression (LLD), the neural correlates have not been clarified.

Neuroimaging studies have provided some evidence of gray matter (Andreescu et al., 2008; Colloby et al., 2011; Du et al., 2014; Lai, 2013; Taylor et al., 2003; Weber et al., 2010; Yuan et al., 2008) and white matter abnormalities (Alexopoulos et al., 2008; Alves et al., 2012; Bae et al., 2006; Bezerra et al., 2012; Charlton et al., 2015; Dalby et al., 2010; Guo et al., 2014; Shimony et al., 2009; Taylor et al., 2007) in LLD. For instance, a meta-analysis of voxel-based morphometry (VBM) studies demonstrated that, compared to healthy individuals, patients with LLD show significantly smaller gray matter volume (GMV) in the anterior cingulate cortex (ACC), hippocampus/amygdala complex, parahippocampus, and putamen and larger GMV in the lingual gyrus (Du et al., 2014). A meta-analysis of white matter (WM) integrity using diffusion tensor imaging (DTI) also demonstrated that patients with LLD had lower fractional anisotropy (FA) in the dorsolateral prefrontal cortex and uncinate fasciculus (UF) compared with healthy individuals (Wen et al., 2014). These findings suggest that the orbitomedial prefrontal limbic network is involved in the pathophysiology of LLD. However, to our knowledge, few studies have examined the structural abnormalities of the GMV and WM in patients with LLD. Sexton et al. showed that patients with LLD have reduced WM FA in several regions, but they did not find any differences in GMV or brain function at rest compared to healthy participants (Sexton et al., 2012).

The aim of the present study was to determine whether patients with LLD show abnormal GMV and WM integrity using multiple image analysis techniques. We hypothesized that compared to healthy participants, patients with LLD would show reduced GMV in the orbitomedial prefrontal limbic network, including the ACC, orbitofrontal cortex (OFC), hippocampus, amygdala, caudate, thalamus and putamen. We also expected the patients with LLD to show lower FA and higher mean diffusivity (MD) in the tracts relevant to this network such as the UF. From previous studies (Andreescu et al., 2008; Taylor et al., 2007), we hypothesized that longer duration of illness, earlier onset of illness, or more severe depressive symptoms would be associated with smaller GM volume of orbitofrontal limbic regions and poorer WM integrity in the tracts to these regions such as the UF.

2. Methods

2.1. Participants

We studied 106 participants, including 45 patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria for major depressive disorder (MDD) and 61 healthy participants. Patients were recruited from Yamaguchi University Hospital and referred by clinics and hospitals in the area. Patients were diagnosed by clinical interviews performed by senior psychiatrists, case conferences with psychiatrists, and structured interviews using the Mini International Neuropsychiatric Interview (M.I.N.I., Japanese version 5.0.0) (Otsubo et al., 2005). Subjects also underwent a clinical interview to determine their clinical demographics. Patients with current or a history of substance abuse/dependence or other psychotic illnesses were excluded from the study. Healthy control participants were recruited by word-of-mouth or by placing advertisements in the community. Any healthy subject who had psychiatric illness was excluded via the M.I.N.I. and clinical interviews. They were also excluded if they had an immediate family member with a psychiatric disorder. This study was carried out in accordance with the latest version of the Declaration of Helsinki. The Institutional Review Board of Yamaguchi University Hospital approved this study. Written informed consent was obtained from all participants after providing them with a complete description of the study. The distributions for sex, age, years of education, and vascular risk factors (Baldwin and Tomenson, 1995) were not significantly different between patients with LLD and healthy participants (Table 1). The vascular risk factors were rated as follows (Baldwin and Tomenson, 1995): 0, absent; 1, 'mild' – asymptomatic (e.g., controlled hypertension; clinical evidence of arteriosclerosis); 2, 'moderate' – symptomatic evidence of arterial disease or, if not symptomatic, likely to become so (e.g., poorly controlled hypertension, history of cardiac dysrhythmia requiring treatment, symptomatic angina and/or peripheral vascular disease); 3, 'severe' – active disease (e.g., peripheral vascular disease with amputation, transient ischemic attack, neurological signs compatible with previous stroke). Current mood states were examined using the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (Williams, 1988). Any participant who was left-handed or ambidextrous was excluded from the analysis (Oldfield, 1971). The Global Assessment of Functioning scale (GAF) (American Psychiatric Association, 2000) was used to assess social